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OLANZAPINE AND DIABETIC KETOACIDOSIS: WHAT IS THE UNDERLYING MECHANISM?

Dear Editor:

Recently, Iwaku et al[1] reported a detailed case of olanzapine-related acute-onset Type 1 diabetes with ketoacidosis.[1] They concluded that olanzapine sometimes can cause sudden hyperglycemia that results in precipitating the onset of Type 1 diabetes. In fact, there is no report of olanzapine-induced diabetes with immunological mechanism. We reported a sporadic case of olanzapine-induced rapid-onset Type 2 diabetes with severe hyperglycemia.[2] In our case, the patient was negative for anti-glutamic acid decarboxylase antibodies, and the discontinuation of olanzapine and careful insulin replacement regimen reversed diabetes. A common feature between these two cases is acute-onset severe hyperglycemia. The first presentation of diabetes associated with olanzapine might be diabetic ketoacidosis (DKA), requiring admission to an intensive care unit. Patients exposed to antipsychotics have approximately 10 times increased risk of DKA compared to the general population, and the majority of patients who developed DKA following antipsychotics were treated with olanzapine and clozapine in the first six months of treatment.[3]

The mechanisms underlying the onset of diabetes by olanzapine are reported to be increased peripheral and hepatic insulin resistance that is mainly due to a weight gain effect.[4] These mechanisms might provide olanzapine-induced, slowly progressive glucose intolerance, such as the onset of Type 2 diabetes, but do not explain olanzapine-related acute-onset DKA. The mechanism of rapid-onset diabetes by olanzapine is poorly understood. In clinical research, olanzapine-treated patients with schizophrenia displayed biphasic changes in insulin secretion in a hyperglycemic challenge. Insulin secretion decreased at Week 2 and increased at Week 8 as the body weight increased.[5] Olanzapine might reduce insulin secretion at an early stage of the treatment. Research has shown that olanzapine evoked endoplasmic reticulum (ER) stress, as evidenced by mild activation of the ER stress sensor molecule PKR-like ER kinase (PERK). However, phosphorylation of the alpha subunit of eukaryotic initiation Factor 2, an event immediately downstream of PERK activation, was not observed, resulting in sustained ER stress and beta-cell apoptosis.[6] Olanzapine is thought to directly influence pancreatic beta-cells and impair insulin secretion at an early stage of treatment, which is a mechanism of acute-onset glucose intolerance. Clinicians should consider the risk of DKA when starting treatment with olanzapine. Further research regarding the direct effect of olanzapine on the pancreatic beta-cell is needed.

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With regard,

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